PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application

Inventors: Barlos et al

Group: 1621

Serial No. 10/740,207, filed Dec. 18, 2003
(Case Docket No. 21526)

For: **PROCESS FOR REGENERATING 2-CHLOROTRITYL CHLORIDE RESINS**

DECLARATION UNDER 1.132

Nutley, New Jersey 07110
September 19, 2207

Mail Stop:
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Bernhard Knipp, a citizen and resident of Germany, declare as follows:

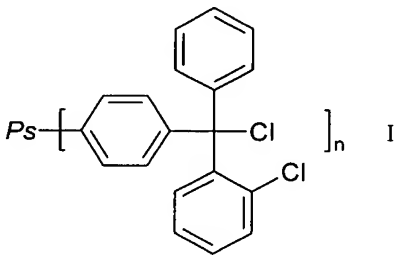
1. From 1982 to 1985, I studied chemistry at the University of Siegen, Siegen, Germany. From 1985 to 1992, I studied chemistry at the University of Cologne, Cologne, Germany. In 1992, I received a PhD from the University of Cologne, Cologne, Germany.

2. From 1992 to 1996, I was a Postdoctoral Fellow, first at the University of Nevada, Reno, USA, then at the Max-Planck-Institute of Radiation Chemistry, Muelheim/Ruhr, Germany and at Boehringer Mannheim GmbH, Mannheim, Germany.

3. From 1996 to present, I have been employed by Boehringer Mannheim GmbH, Mannheim, Germany, which became later to Roche Diagnostics GmbH, Mannheim, Germany, where I have been involved from 1996 to 1997 in chemical

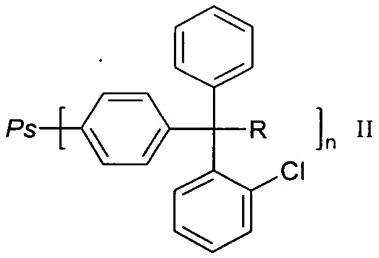
development and from 1997 to 2000 in HR development, training and education and since 2000 as head of a laboratory in chemical and process development.

4. I am familiar with the subject matter of the captioned application, filed Dec. 18, 2003, of which I am a co-inventor. The captioned application is directed to a process for the preparation of solid phase bonded 2-chlorotrityl chloride (2-CTC resin) of formula I:



I

wherein Ps is a polymeric support and n has the following meaning: $1 \geq n > 0$ comprising the reaction of solid phase bonded 2-chlorotrityl of formula II



II

wherein R is OH or/and OC_{1-4}-alkyl or/and NR'R"
wherein R' and R" independently of each other represent C_{1-4}-alkyl, or R' and R" together with the nitrogen to which they are bonded represent a 5 to 8 membered heterocyclic radical.

5. I am familiar with the recent Office Action dated November 3, 2006, in the subject application. I understand that in this Office Action, the subject application is rejected as obvious over the Harre et al. reference of record. Specifically, I understand that the Patent Office alleges that the use of any chlorination agent and solvent would

have been obvious in the claimed invention, compared to the thionyl chloride/organic solvent of the Haare et al. process, absent any unexpected results.

6. I submit this declaration to show that the process of the instant claims is not obvious over the process of the cited reference due to the unexpected results achieved by the process of the instant claims.

7. I supervised the experiments below to compare the process of the present invention using dioxane (as organic solvent) and HCl (as chlorinating agent) with the process of Haare et al (dichloromethane and thionyl chloride) and a process utilizing dioxane and thionyl chloride. The study protocol was as follows:

A) Haare process: In a double-walled jacket reactor with glass frit bottom 10 g used resin (solid phase bonded 2-chlorotrityl of formula II wherein R is OH) was washed once with DMF (100ml) for 30 min and three times with dry methylene chloride (100 ml) for 10 min each and subsequently treated with 1.7 ml (23.4 mmol) thionyl chloride (= 47 mmol Cl) in methylene chloride (100 ml). The mixture was gently stirred for 1 h at room temperature and filtered. The resin was thereafter washed twice with DMF (100 ml) and three times with methylene chloride (100 ml). The activated resin [solid phase bonded 2-chlorotrityl chloride (2-CTC resin) of formula I] was dried under vacuum for 3 h at -18°C and 1 h at room temperature. The content of active chloride of the activated resin [solid phase bonded 2-chlorotrityl chloride (2-CTC resin) of formula I] was 1.4 mol/kg.

B) Dioxane/Thionyl Chloride process: In a double-walled jacket reactor with glass frit bottom 10 g used resin (solid phase bonded 2-chlorotrityl of formula II wherein R is OH) was washed once with DMF (100ml) for 30 min and three times with dry dioxane (100 ml) for 10 min each and subsequently treated with 25 ml (350 mmol) thionyl chloride (= 700 mmol Cl) in dioxane (100 ml). The mixture was gently stirred for 1 h at room temperature and filtered. The resin was thereafter washed twice with DMF (100 ml) and three times with methylene chloride (100 ml). The activated resin [solid phase

bonded 2-chlorotrityl chloride (2-CTC resin) of formula I] was dried under vacuum for 3 h at -18°C and 1 h at room temperature. The content of active chloride of the activated resin [solid phase bonded 2-chlorotrityl chloride (2-CTC resin) of formula I] was 0.8 mol/kg.

C) HCl/Dioxane process: In a double-walled jacket reactor with glass frit bottom 10 g used resin (solid phase bonded 2-chlorotrityl of formula II wherein R is OH) was washed once with DMF (100ml) for 30 min and three times with dry dioxane (100 ml) for 10 min each and subsequently treated with 115 ml dioxane/hydrogen chloride which contained 25 g (700 mmol) HCl_{gas} (= 700 mmol Cl). The mixture was gently stirred for 1 h at room temperature and filtered. The resin was thereafter washed twice with DMF (100 ml) and three times with methylene chloride (100 ml). The activated resin [solid phase bonded 2-chlorotrityl chloride (2-CTC resin) of formula I] was dried under vacuum for 3 h at -18°C and 1 h at room temperature. The content of active chloride of the activated resin [solid phase bonded 2-chlorotrityl chloride (2-CTC resin) of formula I] was 1.8 mol/kg.

In tabular form, the above three experiments (A-C) are depicted for comparison purposes against Table 1, paragraph 24 of the specification, pages 6-8 of the above captioned application:

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formula II R is	solvent	chlorinating agent	T [°C]	t [h]	content of active chloride [mol/kg]
solid phase bonded 2-chlorotrityl of formula II wherein R is OH	100 ml CH2Cl2	1.7 ml SOCl2	25	1	1.4 mol/kg
solid phase bonded 2-chlorotrityl of formula II wherein R is OH	100 ml Dioxane	25 ml SOCl2	25	1	0.8 mol/kg
solid phase bonded 2-chlorotrityl of formula II wherein R is OH	100 ml Dioxane	25 g HCl (gas)	25	1	1.8 mol/kg

8. The summary data for each of the three tests conducted above are depicted below:

Test	Resin (g)	Solvent	Chlorinating Agent (mmol Cl)	Active Chlorine Content
Haare	10 g	100 ml CH2Cl2	1.7 ml SOCl2 (47 mmol Cl)	1.4 mol/kg
Test 2	10 g	100 ml Dioxane	25 ml SOCl2 (700 mmol Cl)	0.8 mol/kg
Test 3	10g	100 ml Dioxane	25 g HCl (gas) (700 mmol Cl)	1.8 mol/kg

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9. The data demonstrate the unexpectedly high active chlorine content of Applicant's invention by the combination of HCl as the chlorinating agent and dioxane as the organic solvent.

10. I further declare that all statements made herein of my knowledge are true and that all statements made on information and belief are believed to be true and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

11.9.07
Date:

Bernhard Knipp
Bernhard Knipp

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